PET-1

IMPACT OF PET-CT IN NEW ERA OF MEDICINE

Positron emission tomography (PET) is a nuclear medicine imaging technique which produces a three-dimensional image or map of functional processes in the body. The system detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule. Images of tracer concentration in 3-dimensional space within the body are then reconstructed by computer analysis. In modern scanners, this reconstruction is often accomplished with the aid of a CT X-ray scan performed on the patient during the same session, in the same machine.

If the biologically active molecule chosen for PET is FDG, an analogue of glucose, the concentrations of tracer imaged then give tissue metabolic activity, in terms of regional glucose uptake. Although use of this tracer results in the most common type of PET scan, other tracer molecules are used in PET to image the tissue concentration of many other types of molecules of interest.

HISTORY & DEVELOPMENT:

First Positron Imaging Device - 1950

The concept of emission and transmission tomography was introduced by David Kuhl and Roy Edwards .In 1950 Chief of the Neurosurgical Service at the Massachusetts General Hospital (MGH) Gordon L. Brownell made suggested that the use of annihilation radiation following positron emission might improve the quality of brain images by increasing sensitivity and resolution. The Physics Research Laboratory (PRL) at MGH had just been established under his direction and, with support from the Neurosurgical Service, a simple positron scanner using two opposed sodium iodide detectors was designed and built within six months. Imaging of patients with suspected brain tumors was commenced almost immediately. The results were sufficiently encouraging that an addendum including results on positron imaging was included in a paper by Sweet on brain tumor localization. During the same year, a paper by Wrenn, Good and Handler [53] described independent studies on annihilation radiation detection.

Despite the relatively crude nature of this imaging instrument, the brain images were markedly better than those obtained by other imaging devices. It also contained several features that were incorporated into future positron imaging devices. Data were obtained by translation of two opposed detectors using coincidence detection with mechanical motion in two dimensions and a printing mechanism to form a two-dimensional image of the positron source.

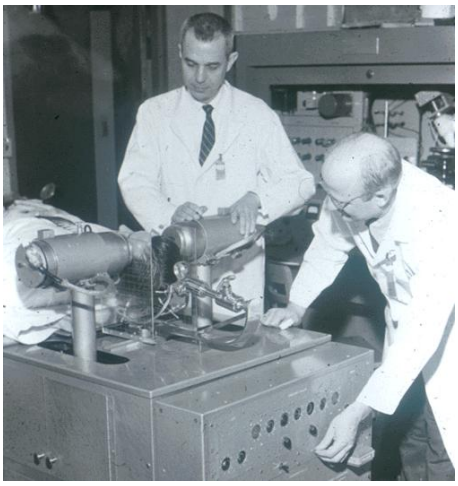

Fig 1: First Clinical Positron Imaging Device

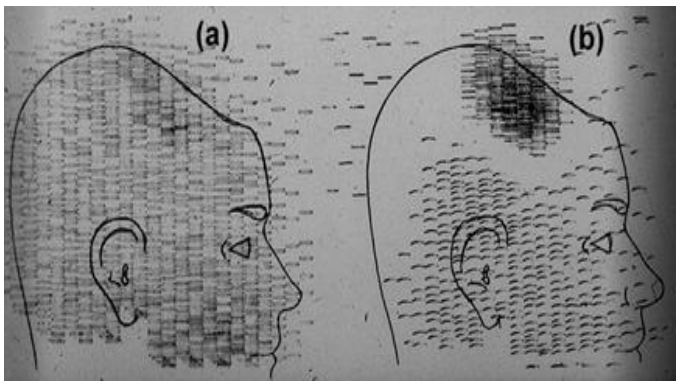

Fig 2 (coincidence and unbalanced scan)

This instrument followed the general concepts of the instrument build in 1950 but included many refinements. It produced both a coincidence scan as well as an unbalance scan. The unbalance of the two detectors was used to create an unbalance image using two symbols to record any unbalance in the single channel rates of the two detectors. The unbalance scan produced a low resolution image but was remarkable sensitive in determining whether a tumor existed, particularly if the tumor was to the right or left of midline of the brain. Figure 2 shows the two scans of a patient with recurring brain tumor.

First Multiple Detector Positron Imaging Device – 1962:

Several versions of the single pair coincidence system were built including a commercial version. It was clear that increased sensitivity was required and a Hybrid Scanner was developed in the mid 60's .This device used two rows of nine detectors each in coincidence with three detectors in the opposite row. The detector assembly translated in one direction so that a two dimensional image was formed. The scanner was designed specifically for brain imaging and served for that purpose in a clinical setting for nearly a decade. A unique feature of the scanner was that in addition to increased sensitivity, another form of three-dimensional image could be obtained by focusing on planes parallel to and lying between the two detector arrays

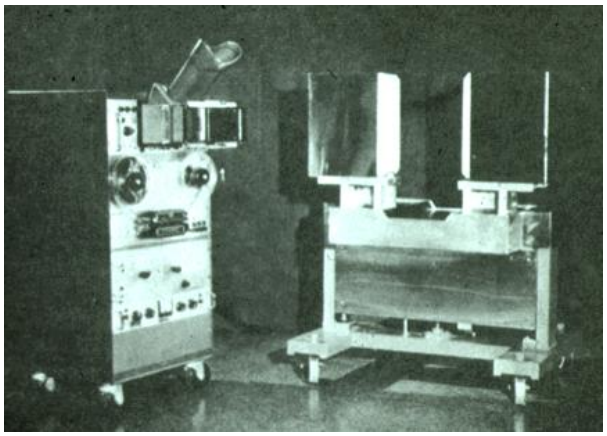

Fig. 3: PC-I The First Tomographic Imaging Device and the First Computed Tomographic Imaging Device (PET): 1968-1971

The logical extension of positron instrumentation was a design using two 2-dimensional arrays. PC-I was the first instrument using this concept and was designed in 1968. The first applications of PC-I in tomographic mode as distinguished from the computed tomographic mode were reported in 1970 (Brownell et al 1970. PC-I incorporated rotation and translation of the two detectorbanks and included interpolative motion of the detectors to improve sampling and image quality. PC-I could produce images on planes parallel to the detector planes or tomographic images on planes within the object. The original intent was to use PC-I to obtain focused images on planes parallel to the detector planes and tomographic images on transverse planes.

In early 1970, David Chesler MGH conceived of filtered back projection. In the summer of 1970 he tested filtered back projection, including the effects of Poisson

noise, by computer simulation. Figure 4 illustrates the concept of filtered back projection and was presented by Chesler at the Meeting on Tomographic Imaging in Nuclear Medicine September 15-16, 1972. This development of filtered back projection was the first reconstruction of this type to be applied to PET and CT data. The filtered back projection algorithm was immediately applied to data from PC-I and the subsequent computed tomographic images were dubbed PET images as an acronym for positron emission tomography

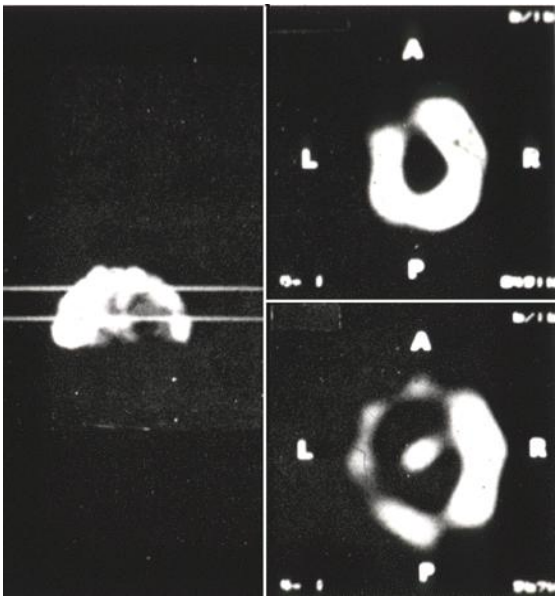

Fig.4: Brain studies using Ga-68 and PC-1

PCR-I and PCR-II: Ring and Cylinder PET Devices:

It soon became clear to many of those involved in PET development that a circular or cylindrical array of detectors was the logical next step in PET instrumentation. Although many investigators took this approach, James Robertson (Robertson et al 1973) and Z.H. Cho (Cho et al 1975) were the first to propose a ring system. The only drawback was the limited sampling provided by these geometries and a number of techniques such as wobbling the array were proposed to increase sampling (Huesman et al 1983). A Donner ring was developed in Berkeley (Derenzo et al 1979) that used a large number of detectors individually coded to small phototubes. However, it was the development of analog coding by Charles Burnham of the PRL at MGH (Burnham et al 1981 and 1985) that permitted the use of multiple small detectors identified by a smaller number of phototubes. The concept was applied to ring and cylindrical arrays to produce high resolution PET images without motion.

This led to the development of two PET systems at MGH, PCR-I (Brownell et al 1985) (Figure 5) and PCR-II (Burnham et al 1988, Brownell et al 1989) (Figure 6). PCR-I used a ring design while PCR-II used a cylindridal design. PCR-I has been in continuous use for sixteen years producing high resolution images in a variety of studies centered on the brain, heart and cancer

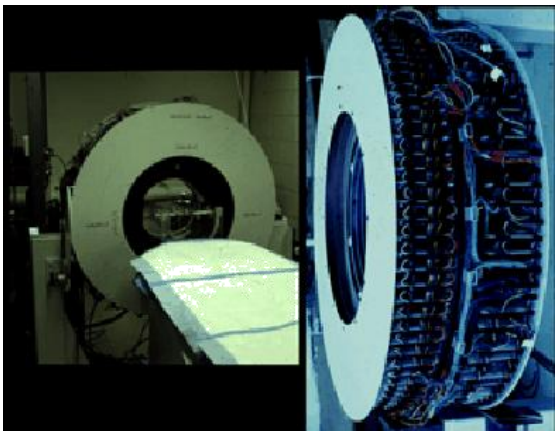

Fig. 5: PCR 1

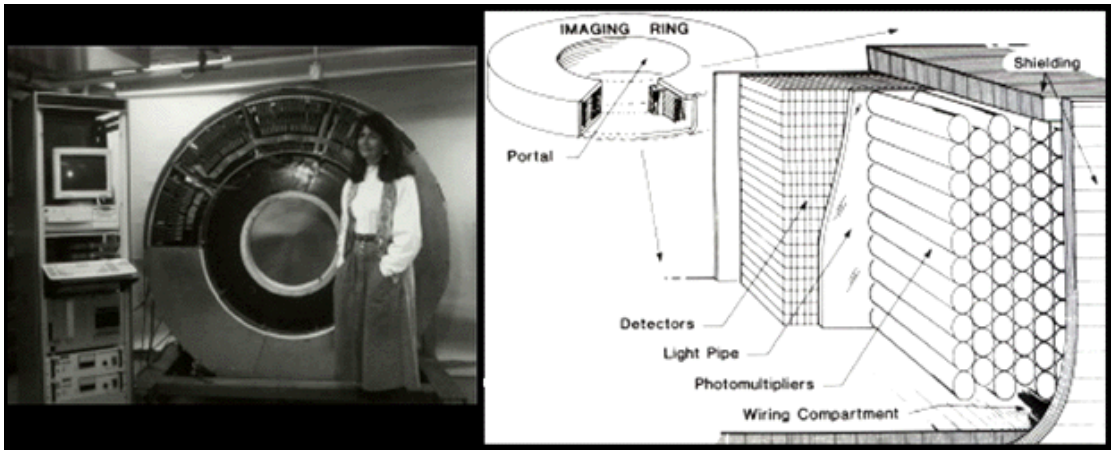

Fig. 6: PCR 2

Radiopharmaceutical Development for PET Imaging:

PET imaging was initially based on the use of ^{15}O labelled to O_2, CO and CO2 primarily because the Allis Chalmers cyclotron in use initially at MGH and Washington University was a deuteron machine and was primarily used to producing^{15}O. More powerful cyclotrons were available in government laboratories such as Brookhaven but it was not until the mid 70's that such cyclotrons became

available to biomedical facilities and the full range of isotopes including ^{11}C, ^{13}N, ^{15}O and ^{18}F became available to a wider audience.

Ter-Pogossian and Powers had demonstrated that ^{15}O labeled water could be used to measure blood flow in brain and other organs long before PET was developed (Ter-Pogossian and Powers 1958 and Ter-Pogossian et al

Oxygen-15 was and remains a very useful label for PET studies and became widely used at MGH for blood flow studies in brain and other organs (Ahluwalia et al 1973, Brownell et al 1976). The application of labeled CO_2 to obtain equilibrium images of blood flow was applied successfully for imaging brain and heart in animals and man (Boucher et al 1976). The use of labeled O_2 together with CO_2 provided the basis for measuring regional oxygen metabolism. 15O labeled CO provided a means of measuring regional blood volume (Brownell and Cochavi 1978). Models were developed to obtain quantitative regional values of these important parameters (Subramanyam et al 1978). The measurement of blood flow and blood volume has become a useful clinical and research tool.

The development of ^{18}F labeled 2-fluorodeoxy-D-glucose (2FDG) by the Brookhaven group under the direction of Al Wolf and Joanna Fowler was a major factor in expanding the scope of PET imaging. The compound was first administered to two normal human volunteers by Abass Alavi in August 1976 at the University of Pennsylvania. Brain images obtained with an ordinary (non-PET) nuclear scanner demonstrated the concentration of FDG in that organ. The half-life of 18F was nearly optimal for positron imaging and it was immediately obvious that 2FDG could give precise values of energy metabolism in brain, heart and other organs (Reivich et al 1979. Michael Phelps further extended the application of 2FDG based on Sokoloff's autoradiographic studies using ^{14}C labeled deoxyglucose (Sokoloff et al 1977). Recent developments in PET radiopharmaceuticals are based on Henry Wagner's pioneering work on imaging with receptors.

Modern Positron emission tomography devices and principles: Operation

To conduct the scan, a short-lived radioactive tracer isotope, which decays by emitting a positron, which also has been chemically incorporated into a biologically active molecule, is injected into the living subject (usually into blood circulation). There is a waiting period while the active molecule becomes concentrated in tissues

of interest; then the research subject or patient is placed in the imaging scanner. The molecule most commonly used for this purpose is fluorodeoxyglucose (FDG), a sugar, for which the waiting period is typically an hour.

As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, the antimatter counterpart of an electron. After travelling up to a few millimeters the positron encounters and annihilates with an electron, producing a pair of annihilation (gamma) photons moving in opposite directions. These are detected when they reach a scintillator material in the scanning device, creating a burst of light which is detected by photomultiplier tubes or silicon avalanche photodiodes (Si APD). The technique depends on simultaneous or coincident detection of the pair of photons; photons which do not arrive in pairs (i.e., within a few nanoseconds) are ignored.

Localization of the positron annihilation event:

The most significant fraction of electron-positron decays result in two 511 keV gamma photons being emitted at almost 180 degrees to each other; hence it is possible to localize their source along a straight line of coincidence (also called formally the line of response or LOR). In practice the LOR has a finite width as the emitted photons are not exactly 180 degrees apart. If the recovery time of detectors is in the picosecond range rather than the 10's of nanosecond range, it is possible to calculate the single point on the LOR at which an annihilation event originated, by measuring the "time of flight" of the two photons. This technology is not yet common, but it is available on some new systems.

Multimodality prototypes:

The proposal to combine PET with CT was made in the early 1990s by Townsend, Nutt and coworkers independently of the Hasegawa work. The suggestion was also made to use the CT images to generate the PET attenuation correction factors.[14] The first prototype PET/CT scanner became operational in 1998,[15] designed and built by CTI PET Systems in Knoxville, TN (now Siemens Molecular Imaging) and clinically evaluated at the University of Pittsburgh. The design incorporated a single-slice spiral CT scanner (Somatom AR.SP; Siemens Medical Solutions, Forchheim, Germany) and a rotating ECAT ART scanner (CTI PET Systems, Knoxville, TN). The PET detectors were mounted on the rear of the CT support and the entire assembly

rotated as a single unit (Fig.7). The data processing included an algorithm[16] to scale the CT images from x-ray energy to PET annihilation photon energy (511 keV) and generate the appropriate attenuation correction factors .The results from the prototype demonstrated the utility of high-resolution anatomic images accurately registered with functional images. The coregistered anatomy localized functional abnormalities and clarified equivocal situations, thus improving the accuracy and confidence of the scan interpretation. The use of a rapidly-acquired, low-noise CT scan in place of a lengthy conventional PET transmission scan improved image quality and reduced scan time.

The first PET/CT prototype evaluated clinically at the University of Pittsburgh. The CT and PET components were mounted on a single rotating support and the data acquired from 2 separate consoles. The CT images were transferred to the PET console and then used for CT-based attenuation correction and localization.

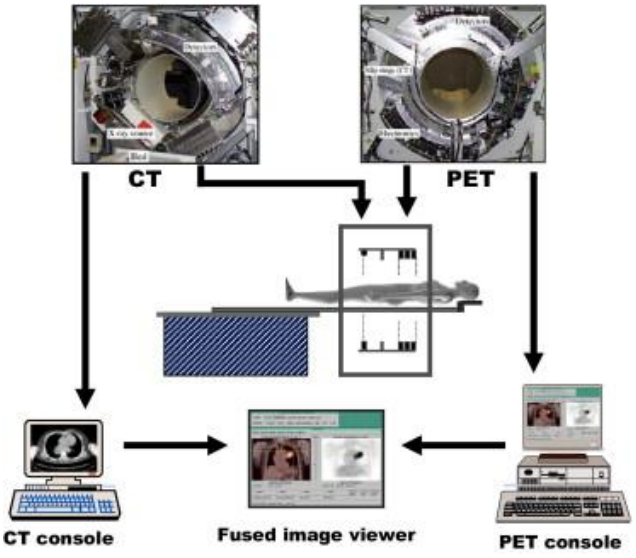

Fig. 7: PET/CT

Current PET/CT Instrumentation:

In 1999, GE Healthcare launched a dual-head scintillation camera combined with a low-power x-ray tube and detectors, called the Hawkeye (GE Healthcare). This design features 2 rectangular sodium iodide camera heads with a 350-W x-ray tube. The Hawkeye was the first commercial scanner to offer combined anatomical and functional imaging in a single unit. Then, less than 2 years after the first Hawkeye

installation, PET/CT scanners incorporating clinical CT and clinical PET performance became commercially available. The first commercial PET/CT scanner to be announced was the Discovery LS (GE Healthcare) in early 2001. This was followed several months thereafter by the release of the Biograph (Siemens Medical Solutions), and then somewhat later by the introduction of the Gemini (Philips Medical Systems). In the past 6 years, PET/CT designs from all vendors have evolved following advances in CT and PET instrumentation. By 2007, 5 vendors worldwide offered PET/CT designs: GE Healthcare, Hitachi Medical, Philips Medical Systems, Toshiba Medical Corporation, and Siemens Medical Solutions. Current designs offered by Siemens Molecular Imaging, GE Healthcare, and Philips Medical Systems are summarized in Figure 8. A recent addition to PET/CT designs is the Gemini TF, the first commercial time-of-flight (TOF) PET scanner. The Gemini TF has yttrium-doped LSO (LYSO) detectors and is combined with a 16- or 64-slice CT scanner. All designs other than the Discovery LS offer a 70-cm-diameter patient port for both CT and PET. All Gemini and Biograph designs acquire PET data in 3D mode only, whereas the Discovery design includes retractable septa and can acquire data in both 2D and 3D mode.

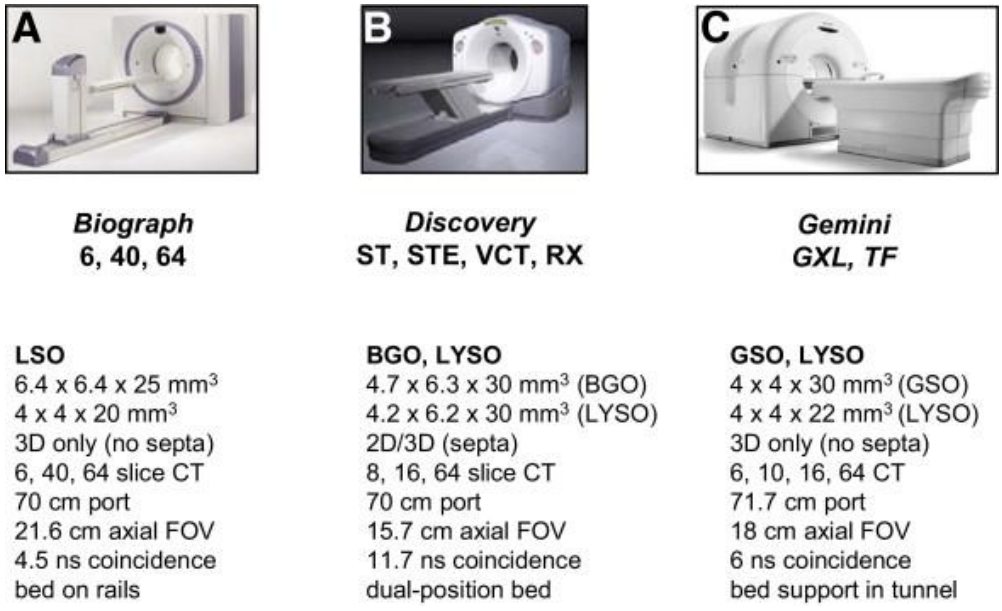

Fig. 8: PET/CT designs of different companies

Multidetector CT Scanners:

After the appearance of single-slice spiral CT scanners in the early 1990s, CT performance has experienced a resurgence with the advent of multi-detector arrays (MDCT). This was accompanied by increases in x-ray power (60 kW or greater) and computer capacity for data processing and image reconstruction. Dual- and 4-slice CT scanners first appeared about 1998, with scan times of 500 ms, followed by 16-slice (2002) and, more recently, 64-slice (2004) devices. The increasing number of detector rows (slices) has been accompanied by faster rotation times so that state-of-the-art scanners can now achieve a full rotation in as little as 330 ms. Spatial resolution has improved from ~10 lines pairs (lp)/cm in 1990 to 25 lp/cm or better today, with slice thicknesses less than 1 mm. A significant innovation that will contribute to increased CT performance is the low-weight Straton x-ray tube. After many years of slow but steady progress, the past decade has seen significant advances in both hardware and software for CT.

New Scintillators for PET:

For PET detectors, the 1970s saw the transition from thallium-activated sodium iodide (NaI(Tl)) to bismuth germanate (BGO), a scintillator with higher density and photofraction. Although at least one PET scanner design continued to use NaI(Tl) until fairly recently, the majority of PET scanners installed during the 1990s were based on BGO block detectors. In the late 1990s, the introduction of new, faster scintillators such as gadolinium oxyorthosilicate (GSO) and lutetium oxyorthosilicate (LSO), both doped with cerium, improved the PET-scanner performance. Both GSO and LSO have shorter decay times than BGO by a factor of 6 to 7, reducing system deadtime and improving count-rate performance, particularly with high activity levels in the FOV. Of even more importance for clinical imaging is the potential of faster scintillators to decrease the coincidence timing window, thereby reducing the random coincidence rate. The increased light output of the new scintillators improves the energy resolution because the increased number of light photons reduces the statistical uncertainty in the energy measurement. However, other physical effects contribute to the emission process and the improvement in energy resolution is not a simple function of the number of light photons. The higher light output also increases the positioning accuracy of a block detector, allowing the blocks to be cut into smaller crystals and thereby improving spatial resolution. BGO, LSO, and GSO are not hygroscopic, facilitating the manufacture and packaging of the detectors. GSO is somewhat more fragile and more difficult to machine than either BGO or LSO. LSO

has an intrinsic activity concentration (of lutetium-177) of ~280 Bq/mL with single-photon emissions in the 88- to 400-keV energy range. Such a radioactive component is of little consequence for coincidence counting at 511 keV, except maybe at very low emission count rates.

Reconstruction Algorithms:

There has been significant progress over recent years in image reconstruction methods through the introduction clinically of statistically based algorithms. Previously, one of the earliest and most widely used 3D reconstruction methods was the re-projection algorithm (3DRP) based on a 3D extension of standard 2D filtered backprojection. Although this algorithm works well for the lower-noise environment of the brain, the quality for whole-body imaging is less than optimal, particularly when rod-source attenuation-correction factors are applied to low-count emission data. Figure 4A, for example, shows a coronal image of a patient with a body mass index of 25 reconstructed using 3DRP. Because CT-based attenuation correction factors have been applied, the image quality is possibly better than would have been obtained with rod-source attenuation-correction factors. The development of Fourier rebinning (FORE) was a breakthrough that enabled 3D data sets to be accurately rebinned into 2D data sets and then reconstructed in 2D with a statistically based expectation-maximization (EM) algorithm. However, it was not until the accelerated convergence achieved by the Ordered-Subset EM (OSEM) algorithm that iterative methods became of clinical interest. Although FORE and OSEM offer improved image quality compared with 3DRP, the incorporation of attenuation-based weights (AWOSEM), as suggested in the original paper by Hudson and Larkin, further improves image quality. This is demonstrated in Figure 9B, where the same data set as in Figure 9A has been reconstructed with FORE and AWOSEM. Further improvement has been achieved by eliminating the rebinning step and implementing OSEM fully in 3D with corrections for randoms, scatter and attenuation incorporated into the system model. The result, again for the same data set, is shown in Figure 9C. Finally, in a recent development termed, “High-Definition (HD)” PET, the detector spatial response function has also been included in the reconstruction model. The point spread function (PSF) varies throughout the FOV owing to the oblique penetration of the detectors by annihilation photons (ie, the depth of-interaction effect). By measuring this variability and then modeling the PSF, improved and near-uniform spatial resolution can be achieved throughout the FOV; the improvement can be seen by comparing Figure 9C with the PSF reconstruction in Figure 9.

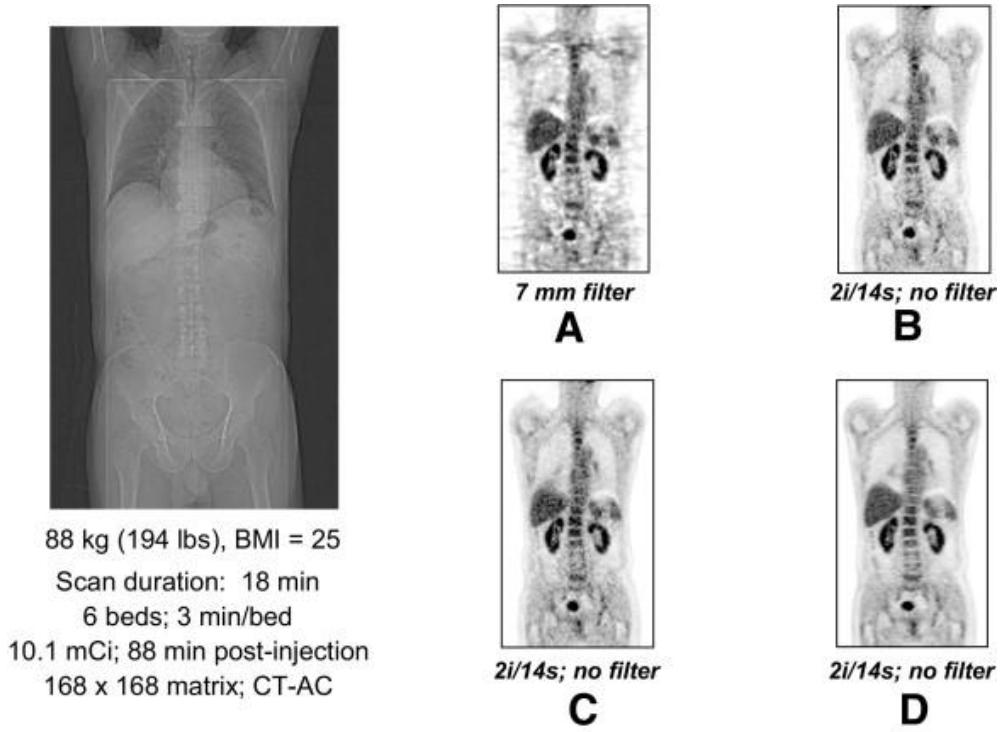

Fig. 9: A coronal section of an FDG-PET whole-body scan of a patient with a body mass index of 25 acquired in 3D mode with septa retracted and reconstructed using: (A) 3D filtered back-projection algorithm with reprojection (7-mm Gaussian smooth); (B) FORE + 2D OSEM (14 subsets, 2 iterations; no smoothing); (C) 3D OP-OSEM (14 subsets, 2 iterations; no smoothing); and (D) HD PET: 3D OSEM with PSF reconstruction (14 subsets, 2 iterations, no smoothing). As noted, all reconstructions except 3DRP are unsmoothed.

Positron Emission Tomography/Magnetic Resonance Imaging: The Next Generation of Multimodality Imaging

PET/CT has certain notable shortcomings, including the inability to perform simultaneous data acquisition and the significant radiation dose to the patient contributed by CT. Magnetic resonance imaging (MRI) offers, compared with CT, better contrast among soft tissues as well as functional-imaging capabilities. Therefore, the combination of PET with MRI provides many advantages that go far beyond simply combining functional PET information with structural MRI information. Many technical challenges, including possible interference between these modalities, have to be solved when combining PET and MRI

Applications:

PET is both a medical and research tool. It is used heavily in clinical oncology (medical imaging of tumors and the search for metastases), and for clinical diagnosis of certain diffuse brain diseases such as those causing various types of dementias. PET is also an important research tool to map normal human brain and heart function.

PET is also used in pre-clinical studies using animals, where it allows repeated investigations into the same subjects. This is particularly valuable in cancer research, as it results in an increase in the statistical quality of the data (subjects can act as their own control) and substantially reduces the numbers of animals required for a given study.

Alternative methods of scanning include x-ray computed tomography (CT), magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI), ultrasound and single photon emission computed tomography (SPECT).

While some imaging scans such as CT and MRI isolate organic anatomic changes in the body, PET scanners, like SPECT are capable of detecting areas of molecular biology detail (even prior to anatomic change). The PET scanner does this via the use of radiolabelled molecular probes that have different rates of uptake, depending on the type and function of tissue involved. The changing of regional blood flow in various anatomic structures (as a measure of the injected positron emitter) can be visualized and relatively quantified with a PET scan.

PET imaging is best performed using a dedicated PET scanner. However, it is possible to acquire PET images using a conventional dual-head gamma camera fitted with a coincidence detector. The quality of gamma-camera PET is considerably lower, and acquisition is slower. However, for institutions with low demand for PET, this may allow on-site imaging, instead of referring patients to another center, or relying on a visit by a mobile scanner.

PET is a valuable technique for some diseases and disorders, because it is possible to target the radio-chemicals used for particular bodily functions.

Oncology: PET scanning with the tracer fluorine-18 (^{18}F) fluorodeoxyglucose (FDG), called FDG-PET, is widely used in clinical oncology. This tracer is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase (whose mitochondrial form is greatly elevated in rapidly-growing malignant tumours).

A typical dose of FDG used in an oncological scan is 200-400 MBq for an adult human. Because the oxygen atom which is replaced by ^{18}F to generate FDG is required for the next step in glucose metabolism in all cells, no further reactions occur in FDG. Furthermore, most tissues (with the notable exception of liver and kidneys) cannot remove the phosphate added by hexokinase. This means that FDG is trapped in any cell which takes it up, until it decays, since phosphorylated sugars, due to their ionic charge, cannot exit from the cell. This results in intense radiolabeling of tissues with high glucose uptake, such as the brain, the liver, and most cancers. As a result, FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, particularly in Hodgkin's disease, non Hodgkin's lymphoma, and lung cancer. Many other types of solid tumors will be found to be very highly labeled on a case-by-case basis-- a fact which becomes especially useful in searching for tumor metastasis, or for recurrence after a known highly-active primary tumor is removed. Because individual PET scans are more expensive than "conventional" imaging with computed tomography (CT) and magnetic resonance imaging (MRI), expansion of FDG-PET in cost-constrained health services will depend on proper health technology assessment; this problem is a difficult one because structural and functional imaging often cannot be directly compared, as they provide different information. Oncology scans using FDG make up over 90% of all PET scans in current practice.

Neurology: PET neuroimaging is based on an assumption that areas of high radioactivity are associated with brain activity. What is actually measured indirectly is the flow of blood to different parts of the brain, which is generally believed to be correlated, and has been measured using the tracer oxygen-15. However, because of its 2-minute half-life ^{15}O must be piped directly from a medical cyclotron for such uses, and this is difficult. In practice, since the brain is normally a rapid user of glucose, and since brain pathologies such as Alzheimer's disease greatly decrease brain metabolism of both glucose and oxygen in tandem, standard FDG-PET of the brain, which measures regional glucose use, may also be successfully used to differentiate Alzheimer's disease from other dementing processes, and also to make early diagnosis of Alzheimer's disease. The advantage of FDG-PET for these uses is

its much wider availability. PET imaging with FDG can also be used for localization of seizure focus: A seizure focus will appear as hypometabolic during an interictal scan. Several radiotracers (i.e. radioligands) have been developed for PET that are ligands for specific neuroreceptor subtypes such as [^{11}C] raclopride and [^{18}F] fallypride for dopamine D2/D3 receptors, [^{11}C]McN 5652 and [^{11}C]DASB for serotonin transporters, or enzyme substrates (e.g. 6-FDOPA for the AADC enzyme).

These agents permit the visualization of neuroreceptor pools in the context of a plurality of neuropsychiatric and neurologic illnesses. A novel probe developed at the University of Pittsburgh termed PIB (Pittsburgh Compound-B) permits the visualization of amyloid plaques in the brains of Alzheimer's patients. This technology could assist clinicians in making a positive clinical diagnosis of AD pre-mortem and aid in the development of novel anti-amyloid therapies.

Cardiology, atherosclerosis and vascular disease study: In clinical cardiology, FDG-PET can identify so-called "hibernating myocardium", but its cost-effectiveness in this role versus SPECT is unclear. Recently, a role has been suggested for FDG-PET imaging of atherosclerosis to detect patients at risk of stroke.

Neuropsychology / Cognitive neuroscience: To examine links between specific psychological processes or disorders and brain activity.

Psychiatry: Numerous compounds that bind selectively to neuroreceptors of interest in biological psychiatry have been radiolabeled with C-11 or F-18. Radioligands that bind to dopamine receptors (D1,D2, reuptake transporter), serotonin receptors (5HT1A, 5HT2A, reuptake transporter) opioid receptors (mu) and other sites have been used successfully in studies with human subjects. Studies have been performed examining the state of these receptors in patients compared to healthy controls in schizophrenia, substance abuse, mood disorders and other psychiatric conditions.

Pharmacology: In pre-clinical trials, it is possible to radiolabel a new drug and inject it into animals. The uptake of the drug, the tissues in which it concentrates, and its eventual elimination, can be monitored far more quickly and cost effectively than the older technique of killing and dissecting the animals to discover the same information. PET scanners for rats and non-human primates are marketed for this purpose. The technique is still generally too expensive for the veterinary medicine

market, however, so very few pet PET scans are done. Drug occupancy at the purported site of action can also be inferred indirectly by competition studies between unlabeled drug and radiolabeled compounds known apriori to bind with specificity to the site.

Molecular Imaging : Molecular imaging can be defined as “the visual representation, characterization and quantification of biological processes at the cellular and subcellular level.”[1] Imaging techniques available for this purpose include nuclear medicine techniques (in particular positron emission tomography [PET]), magnetic resonance imaging (MRI) with dedicated imaging sequences and molecular contrast agents, and optical imaging (including bioluminescence and immunofluorescence imaging). The goals of molecular imaging include:

• To improve our understanding of tumor biology (cancer development, progression, and metastasis).

• To visualize and quantify noninvasively the presence and biologic status (active/inactive) of receptors and pathways involved in tumor development and progression.

• To study the pharmacokinetics and pharmacodynamics of novel anticancer “targeted therapies”.

• To measure and predict the response to such novel anticancer drugs early during the therapy. (Here, one would particularly like to know how sensitive and specific the molecular imaging information is and whether molecular imaging as part of treatment monitoring will ultimately improve patient outcome, for instance, by avoiding side effects from continued drug exposure if that drug has no therapeutic efficacy or when secondary resistance develops.)

Molecular imaging thus differs greatly from anatomic imaging, which is used to visualize structural abnormalities that are usually already the endpoint of the underlying molecular process. The need for molecular imaging has also been recognized by radiation oncologists. Traditionally, radiation therapy design has been based on the concepts of the anatomically defined gross tumor volume (GTV), planning target volume (PTV), and clinical target volume (CTV). However, it has become obvious that target design based on structural abnormalities alone has many

limitations, leading to overtreatment of healthy tissues or undertreatment of sites of disease. The new concept of a biologic target volume (BTV) therefore also considers functional parameters that may affect the response to irradiation, such as cancer metabolism, proliferation and hypoxia

Glucose Metabolism

Fatty Acid Metabolism

Proliferation :^{11}C thymidine

Hypoxia and Angiogenesis ^{18}F-FMISO ,^{18}F EF-5,[115] ^{60}Cu-ATSM,[116] ^{18}F-FETNIM, and ^{18}F-FAZA.[117]

Apoptosis :^{18}F annexin

Radiotherapy treatment planning: Radiation therapy has evolved from 2-dimensional (2D) to 3-dimensional (3D) treatments and, more recently, to intensity-modulated radiation therapy and image-guided radiation therapy. Improvements in imaging have enabled improvements in targeting and treatment. As computer-processing power has improved during the past few decades, it has facilitated developments in both imaging and treatment. FDG-PET and PET/CT imaging appears useful in improving radiotherapy treatment planning because of its greater accuracy in identifying nodal (N3) and distant metastatic disease, which precludes surgery and allows better RT delivery. The incorporation of the FDG-PET into treatment volume determination can increase or decrease the treated volume between 15 to 60%. FDG-PET imaging is not perfect and false positives and negatives should be taken into consideration during treatment planning. FDG-PET thresholding needs further study to optimize the levels depending on tumor size, location and heterogeneity. Solutions such as PET gating, 4DCT, and average CT techniques allow improvements in quantification and correct image misregistration. Follow-up data obtained from FDG-PET/CT for treatment planning shows promise, but the actual improvement in outcomes needs to be demonstrated. Novel tracers can be used to identify the hypoxic and presumed radioresistant volume of tumor, which may potentially benefit from more intense or higher doses of radiation to this tumor fraction with the hope of improving patient response or outcome.

Tumor Biology-Guided Radiotherapy Treatment Planning: Gross Tumor Volume Versus Functional Tumor Volume: The ultimate goal of the partnership between

nuclear medicine physicians and radiation oncologists is to use this information with absolute clarity in target definition for radiation treatment planning and therapy, as well as response evaluation. Functional imaging can provide metabolic information and behavioral correlation along with the anatomical imaging for correlative target delineation. Additionally, as a purely diagnostic instrument, PET/CT provides a tool for oncologists to make critical decisions regarding radiation treatment planning modifications secondary to changes in tumor staging (up or down), treatment field modifications, localized control, sites of residual and/or metastatic disease and post therapy response evaluation.

Conclusion:

There is little doubt that, during the past years, PET/CT has had a growing impact on clinical imaging and particularly in oncology in staging and restaging disease and monitoring response to therapy. Although the technology has been somewhat disruptive in the sense that it has brought together medical specialties that have not traditionally worked together, namely, nuclear medicine and radiology, the overall impact has been positive. To meet the demand for cross-training of both the technologists who operate the devices and the physicians who interpret the studies, guidelines have been published[121] and new standards established, leading to a somewhat different situation today from the way radiology and nuclear medicine have traditionally functioned. This trend is likely to continue as other multimodality devices reach the clinic, including SPECT/CT (introduced in 2004) and MR/PET (currently under development).

Recommended readings:

PET: Molecular Imaging and Its Biological Applications Michael E. Phelps
RCNA January 2005 PET Imaging II
RCNA November 2004 PET Imaging I
Volume 38, Issue 3 pp. 149-222 (May 2008) Developments in Instrumentation
Seminar in Nuclear Medicine Volume 38, Issue 2 pp. S1-S46, 103-148 (March 2008) Role of Positron Emission Tomography in Radiation Oncology
Seminar in Nuclear Medicine Volume 37, Issue 6 – selected pp. 399-488 (November 2007) Positron Emission Tomography with Fluorine-18 Agents Other Than Fluorodeoxyglucose

Seminar in Nuclear Medicine Volume 34, Issue 4 – selected pp. 241-329 (October 2004) Positron Emission Tomography, Part III

Seminar in Nuclear Medicine Volume 34, Issue 3 pp. 165-240 (July 2004) Positron Emission Tomography, Part II

Seminar in Nuclear Medicine Volume 28, Issue 4 – selected pp. 277-368 (October 1998) The Coming Age of Pet (Part 2)

Seminar in Nuclear Medicine Volume 28, Issue 3 pp. 199-276 (July 1998) The Coming Age of Pet (Part 1)